Applicant respectfully requests that a copy of Forms 1449, listing all references that were submitted with the Information Disclosure Statements filed on May 5, 2000 and September 5, 2000, be marked as considered and initialed by the Examiner, and be returned with the next official communication.

The 35 U.S.C. § 102 and § 103 Rejections

The Examiner rejected claims 1-4, 8, 11, 13, 17, 31, and 34-35 under 35 U.S.C. § 102(e) as being anticipated by Weiner et al. (U.S. Patent No. 6,077,509). The Examiner also rejected claims 2, 6, 8-9, 13, 34, and 37 under 35 U.S.C. § 102(e) as being anticipated by King (U.S. Patent No. 6,106,844). The Examiner further rejected claims 1-5, 8, 11-12, 31, and 34-36 under 35 U.S.C. § 102(e) [*sic*] as being anticipated by Daniel et al. (Proc. Natl. Acad. Sci. U.S.A., 93, 956-960 (1996)). In addition, the Examiner rejected claims 17-18 and 41 under 35 U.S.C. § 103(a) as being unpatentable over Daniel et al. These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

Weiner et al. disclose that experimental allergic encephalomyelitis (EAE) is an animal model for multiple sclerosis (MS) that can be induced by immunization with myelin basic protein (MBP) or by injection of $CD4^+$ MBP reactive T cells (column 2, lines 14-19). Weiner et al. disclose the use of peptides of human MBP as immunosuppressive agents (column 4, line 66-column 5, line 3), which can be administered intravenously, orally, subcutaneously, intraperitonally or by inhalation (column 8, line 66 to column 9, line 2, and column 11, lines 29-30 and 58-64).

It is also disclosed that T cells that induce EAE are termed encephalitogenic cells, and they specifically recognize peptides corresponding to the immunodominant regions of MBP (column 2, lines 23-26). To test the efficacy of a peptide-based therapy, Weiner et al. orally or intravenously administered MBP peptides encompassing encephalitogenic residues 71-90 (SLPQKSQRSQDENPEHF), nonencephalitogenic residues 21-40 (MDHARHGFLPRHRDTGILDS), or residues 151-170 (GTLSKIFKLGGRDSRS), to female Lewis rats (an inbred strain), followed by immunization of those rats with guinea pig MBP. It is disclosed that suppression of EAE via i.v. tolerization only occurred with whole MBP and

residues 71-90 not with residues 21-40, while suppression of EAE via oral tolerization occurred with either residues 21-40 or residues 71-90 (column 22, lines 25-29). Interestingly, the same peptide administered by a different route, i.e., residues 21-40, had the opposite effect. Also note that the sequences of the suppressive peptides for rats were unrelated to the sequence of peptides which reacted with MBP reactive T cell lines from MS patients (n=23), i.e., residues 84-102 of MBP (ENPVVHFFKNIVTPRTPPPS; Figure 10), or residues 143-168 of MBP (FKGVDAQGTLSKIFKLGGRD; Table 1) (column 15, line 45-52).

As noted at column 3, lines 4-5 of Weiner et al., MS is a T cell-mediated autoimmune disease. Thus, Weiner et al. relate to peptide-based therapies for T cell-mediated disorders not an antibody-mediated disease (claims 1, 2 and 17).

Moreover, as one of the two peptides tested in rats by Weiner et al. had a different effect when administered by an i.v. versus an oral route, Weiner et al. fail to evidence that respiratory administration of a peptide would be useful to treat any disease, much less an antibody-mediated disease. Nor do Weiner et al. teach a method to suppress, tolerize or inhibit the priming or activity of CD4+ T cells which are associated with aberrant, pathogenic or undesirable antibody production specific for an exogenous antigen. Hence, Weiner et al. do not teach Applicant's invention.

King discloses immunogenic peptides from vespid antigen 5 and the use of T cell epitopes of vespid antigen 5 to anergize T cell responses in sensitive individuals (abstract). Immunodominant vespid antigen 5 peptides are disclosed as useful in immunotherapy, e.g., via subcutaneous injection or intranasal administration (column 27, line 44-column 28, line 8). It is further disclosed that peptides that are antigenic in more than one mouse strain are candidates for immunodominant epitopes in antigen 5 sensitive humans (column 18, lines 51-55). However, the Examiner is requested to consider that even if a universal epitope peptide for a certain antigen in mice was identified, it is unlikely that the same peptide has a universal epitope for humans as the immune response loci for mice (HLA) are quite different and much less complex that the immune response loci of humans (MHC).

Peptides of antigen 5 were contacted with spleen cells from five strains of mice (Figures 4-14 and Example 1). Interestingly, although three antigen 5 peptides were recognized by 3/5

strains (60%), no peptide was recognized to a significant extent by spleen cells from all five strains of mice or even by spleen cells from 4/5 strains of mice.

King does not provide any data relating to the impact of the administration of peptides on antibody production, much less the impact of respiratory administration of peptides on antibody production. In this regard, the Examiner is requested to consider that in Norman et al. (Am. J. Resp. Crit. Care Med., 154, 1623 (1996), a reference cited against the claims in the Office Action dated February 18, 1999 under § 102(b)), the subcutaneous administration to humans of two T cell reactive peptides for allergens in cat dander (Fel1 and Fel2) resulted in a decrease in nose and lung symptoms in two groups treated with the peptides, but that none of the treated groups "showed a significant change in IgE or IgG antibody to Fel d 1" (page 1626, Table 1). Thus, T cell epitope peptide administration does not necessarily result in a decrease in aberrant, pathogenic or undesirable antibody production.

Further, prior to Applicant's disclosure, it was unclear whether antigen or peptide administration would be efficacious for an antibody-mediated disease for two reasons. First, while effective at reducing antigen-specific CD4+ responses, administration of antigen through routes that downregulate CD4+ responses may directly stimulate B cells specific for the administered antigen (see page 2 of Applicant's specification). This stimulation may have disastrous consequences, as has been shown in marmoset EAE, where intraperitoneal administration of myelin resulted in CD4+ tolerance to myelin, but also in an acute, fatal form of EAE. The fatal form of EAE was characterized by antibody specific for the myelin oligodendrocyte glycoprotein. Second, administration of antigen through routes that stimulate Th2 cells and downregulate proinflammatory Th1 cells can stimulate antibody synthesis and cause exacerbation rather than improvement of antibody-mediated autoimmune diseases. This concern was also noted in Norman et al. with respect to the use of peptides for tolerization (i.e., peptides must be carefully selected to avoid peptides having tertiary structures recognized by IgE antibodies). Thus, King does not disclose Applicant's invention.

Daniel et al. disclose that insulin-dependent diabetes mellitus (IDDM) is an autoimmune disorder in which insulin-producing beta cells are specifically destroyed and that nonobese diabetic (NOD) mice, which develop IDDM, are a model for type I diabetes (page 956). It is also

disclosed that while insulin autoantibodies (IAA) precede the onset of diabetes the available data indicate that T cells are the dominant mediators of beta cell destruction (page 956). Thus, IDDM is a T cell-mediated disease, not an antibody-mediated disease.

Daniel et al. also disclose that in NOD mice, the T cell response to insulin is dominated by the response to residues 9-23 of the B chain of insulin (B-(9-23)) (page 956). To further characterize the insulin response of NOD mice, Daniel et al. determined that 93% of 312 insulin-specific T cell clones obtained from 21 mice responded to B-(9-23). Such a result should not be surprising given that these mice are inbred. It was also found that administration of B-(9-23) to 4 week old female NOD mice via a single subcutaneous injection or multiple intranasal exposures reduced the percent of mice with increased blood glucose levels (Figures 3 and 4). Daniel et al. further found that intranasal administration of B-(9-23) for five consecutive days decreased the lymph node cell proliferative response (page 958).

While Daniel et al. suggest that "[i]ntranasal administration of insulin or insulin peptides may be of value for prevention of type I diabetes in human subjects" (page 960), they point out that a study reported by Keller et al. (Lancet, 341, 927 (1993), a copy is enclosed herewith), where protection was observed after subcutaneous low dose and intravenous insulin administration to subjects at risk for IDDM, "involved relatively small group sizes and awaits confirmation" (page 960). Keller et al. measured blood levels of islet cell and insulin autoantibodies, fasting blood glucose, and first phase insulin release in these patients. Daniel et al., however, question the efficacy of insulin-based therapies as results reported by Keller et al. were obtained using human peripheral blood, which are "of questionable relevance to the disease process" (page 960). Hence, Daniel et al. do not disclose Applicant's invention.

Accordingly, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 102.

With respect to the § 103 rejection, the Examiner asserts that one of ordinary skill in the art at the time the invention was made would have been motivated to substitute mice for humans as taught by Daniel et al., because it is art recognized that mouse models are used to gain insight for future human therapeutic use. The Examiner further asserts that from the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable

expectation of success in producing the claimed invention.

Daniel et al. provide no motivation to employ peptide therapy for an antibody-mediated disease as Daniel et al. relate to a T cell-mediated disorder.

Further, although Daniel et al. report that nasal administration of a peptide decreased the lymph node proliferative response and blood glucose levels in mice immunized with insulin-derived peptides, the results were obtained in a model for a T cell-mediated disease which employed inbred mice, and those results cannot be employed to predict success for an antibody-mediated disorder or for non-inbred organisms. Therefore, the art worker in possession of the cited art would have no reasonable expectation that respiratory administration of a peptide can prevent or inhibit an indication associated with aberrant, pathogenic or undesirable antibody production in mammals that are divergent at their immune response loci.

Therefore, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6959) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date September 5, 2002 By _____
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Reg. No. 39,665

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 5th day of September, 2002.

Dawn M. Poole
Name

Dawn M. Poole
Signature

Docket No. 00600.423US1
WD # 460831.wpd

U of M File No. 96026

Clean Version of Pending Claims

METHODS TO TREAT UNDESIRABLE IMMUNE RESPONSES
Applicant: Bianca M. Conti-Fine
Serial No.: 08/991,143

1. A method of preventing or inhibiting an indication or disease associated with aberrant, pathogenic or undesirable antibody production which is specific for a particular endogenous antigen, comprising: administering to the respiratory tract of a human afflicted with, or at risk of, the indication or disease a dosage form comprising an amount of at least one epitope peptide, wherein the administration of the dosage form is effective to alter the aberrant, pathogenic or undesirable antibody production in humans having divergent HLA haplotypes, wherein the sequence of the epitope peptide comprises a universal, immunodominant epitope, and wherein the peptide comprises less than the sequence of the endogenous antigen.

2. (Five times amended) A method of suppressing, tolerizing or inhibiting the priming or activity of $CD4^+$ T cells which are associated with aberrant, pathogenic or undesirable antibody production specific for an exogenous antigen, comprising: administering to the respiratory tract of a mammal afflicted with, or at risk of, the indication or disease a dosage form comprising an amount of at least one epitope peptide, wherein the administration of the dosage form is effective to suppress, tolerize or inhibit the priming or activity of, CD4+ T cells which are associated with said antibody production, thereby reducing or inhibiting the amount of said antibody, in mammals having divergent immune response haplotypes, wherein the CD4+ T cells are specific for the exogenous antigen, wherein the sequence of the epitope peptide comprises a universal, immunodominant epitope sequence, and wherein the peptide comprises less than the sequence of the antigen.

3. The method of claim 1 wherein the administration is effective to reduce or inhibit the amount of said antibody for an antigen comprising said peptide.

H2 Sub I, 5. (Amended) The method of claim 1 wherein the endogenous antigen is the acetylcholine receptor, insulin, growth hormone, factor VIII or factor IX.

H3 Sub I, 7. (Amended) The method of claim 2 wherein the exogenous antigen is a fungal antigen.

16. The method of claim 2 wherein the antigen is an exogenous antigen from a domestic cat.

H4 Sub I, 17. (Five times amended) A method to tolerize a human to an endogenous antigen associated with aberrant, pathogenic or undesirable antibody production in the human, comprising: administering to the respiratory tract of the human at least one epitope peptide, having a universal immunodominant epitope sequence, wherein the administration is effective to tolerize $CD4^+$ cells which are associated with antibody production to the endogenous antigen, in humans having divergent HLA haplotypes and wherein the peptide comprises less than the sequence of the antigen.

18. The method of claim 17 wherein the peptide is nasally administered.

31. The method of claim 1, 2, or 17 wherein the administration does not increase synthesis of pathogenic antibody to the native antigen.

34. The method of claim 1 or 2 wherein the administration is effective to reduce or inhibit the affinity of the antibody for an antigen comprising said peptide.

35. The method of claim 34 wherein the antigen is an endogenous antigen.

36. The method of claim 35 wherein the endogenous antigen is the acetylcholine receptor, insulin, growth hormone, factor VIII or factor IX.

37. The method of claim 34 wherein the antigen is an exogenous antigen.

38. The method of claim 37 wherein the antigen is a fungal antigen.

39. The method of claim 1, 2 or 17 further comprising administering an agent that inhibits B cell activation.

41. The method of claim 17 wherein the endogenous antigen is the acetylcholine receptor, insulin, growth hormone, factor VIII or factor IX.

H5 Sub I, 1

42. (Amended) The method of claim 1 wherein the peptide includes residues 150-169, 181-200 or 360-378 of the *Torpedo californica* acetylcholine receptor alpha subunit or a portion of those residues.

43. The method of claim 42 wherein the mammal is a mouse.

H6 Sub I

44. (New) The method of claim 1 or 17 wherein the antigen is factor VIII.